REMARKS

Claims 1-12 currently are pending. Claims 5-12 are withdrawn from further consideration by the examiner as being drawn to a non-elected invention.

Restriction requirement

The examiner found the applicants' arguments convincing with regards to claims 3 and 4 (Group II). However, the examiner withdrew claims 5-12 as being drawn to a non-elected invention.

Applicants further traverse the restriction requirement. Applicants believe the subject matter of claims 5-12 relate to the same invention as of claims 1 and 2 because claims 1 and 2 relate to general compositions whereas claims 8-12 relate simply to preferred realizations of said compositions such as food and nutritional substances. The preferred applications "food" and "nutritional substances" are based on the advantageous effect of the compositions claimed in claims 1 and 2.

This reasoning applies to claims 5-7 (Group III). The inhibition of COX would be useful in the treatment of the listed diseases. The application of the compositions in such a treatment is just a narrowing of the general usage of the compositions which is based on the observed advantageous effect.

IDS

Applicants herein submit a supplemental IDS and Certification of Recent Discovery.

35 USC § 112, second paragraph

The examiner rejected claims 1-4 under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

which applicant regards as the invention. The examiner stated that in the present instance, claim 1 recites the broad recitation "R^5, R^6, R^7, R^8 represent independently of each other Hydrogen, Hydroxy or Methoxy", and the claim also recites "a sugar substituent like glucoside, rutinoside..." The examiner believes this is a narrower statement of the range/limitation. However, "R^5, R^6, R^7, R^8 represent independently of each other Hydrogen, Hydroxy or Methoxy" does not comprise sugar substituents and therefore is not narrowed by the further recitation of sugars.

Applicants delete "like glucoside, rutinoside, manno glucoside, rutinoside, manno gluco pyranosyl, aprosylglucoside" in claim 1 to overcome the examiner's rejection.

The examiner stated that in claim 1, line 19, the Markush group "manno gluco pyranosyl" is vague and indefinite in that the chemical nomenclature is not seen to be conventional and is inconsistent with a sugar substituent. The examiner stated that the same error could be found in the specification and abstract. Applicants replace "manno gluco pyranosyl" with "manno/gluco-pyranosyl". The support for this amendment is found in table 1, last line and also in table 3.

Applicants amend claims 3 and 4 as suggested by the examiner.

35 USC § 103(a)

Claims 1-4 are rejected under 35 USC § 103(a) as being unpatentable over Nair et al. (US 6,194,469) in view of Yoshikumi et al. (US 4,440,757).

Applicants amend claim 1 so that $R^{4'}$ is H, flavone, 5-OH-flavone, 7-OH-flavone and 7,8-(OH)2-flavone. Nair et al. and Yoshikumi et al. taken individually or together do not teach nor suggest claim 1 as invented. Compounds of the formula I or II wherein $R^{4'}$ is H, flavone, 5-OH-flavone, 7-OH-flavone and 7,8-(OH)2-flavone have the advantageous effect of inhibiting biosynthesis of COX-2 and NFxB.

The examiner states that claims 1-4 of the present application are directed to a "composition for inhibiting cyclooxygenase (COX) enzymes." (page 4 of office action). On page 5, second paragraph, the examiner states hat "the applicant's use of formula I and II where a glucoside is attached to C-7 position in a flavonoid for inhibiting COX-2 biosynthesis according to claim 3 and 4 is seen to be rendered obvious, see col. 11, lines 29-34 of Nair et al., wherein the inhibitory activity of C-7 glucosylated genistin isoflavonoid is disclosed." Therefore, it appears that the examiner does not discriminate between the inhibition of an enzyme and the inhibition of the **biosynthesis** of the enzyme. The present invention relates to compositions for the inhibition of COX 2- and NFxb-biosynthesis, and therefore the inhibition of the production of the protein in a cell via processes such as transcription, translation etc.. The subject the present invention does not relate to the inhibition of the product of this process, the proteins COX 2- and NFxb.

The state of the art cited by the examiner relates to a composition and a method for "inhibiting cyclooxygenase enzymes using a mixture of anthocyanins, bioflavonoids and phenolics." (page 5, second paragraph of the office action). As the examiner correctly states, Nair et al. disclose the inhibitory activity to the protein but Nair et al. do not teach the claimed compounds' inhibitory activity to the biosynthesis of the said enzymes.

In examples 4 to 6, Nair et al. show the inhibitory activity of the claimed compounds in biochemical *in vitro* experiments, biological test systems like cells are not used or mentioned. A person skilled in the art knows that the inhibitory effect of the compounds shown in Nair et al. are effects due to a direct interaction between the protein and the inhibitor in the *in vitro* experiment. The inhibitor will probably bind to the

active site of the protein or to a site which plays an important role in the protein's stability or structure. Thus, a person skilled in the art would not assume that the compounds shown in Nair et al. would have any other effect than an interaction with the protein. Moreover, the cited state of the art does not disclose any biosynthesis-inhibitory function of the compounds of formula I or II, not to mention COX 2- and NFκb. Finally, it is very surprising that compounds which are known to inhibit the activity of a protein are able to inhibit the synthesis of not only enzymes of the same cellular pathway but the enzyme itself.

The examiner further refers to Yoshikumi et al. as "regulating prostaglandins." As the examiner correctly states on page 6, second paragraph, Yoshikumi et al. do not provide specific disclosure regarding the use of a bioflavoid (or any other compound of the present application) in the inhibition of a cyclooxygenase. However, also the present application does not disclose any compound for the inhibition of a cyclooxygenase. Applicants' invention only relates to the inhibition of its biosynthesis. Moreover, Yoshikumi et al. merely teach pharmaceutical compounds for the regulation of prostaglandins which have no structural feature in common with the compounds disclosed in the present application. It is not surprising that compounds exist, which regulate the prostaglandin levels.

Nair et al. and Yoshikumi et al. both relate to a different type of compounds and do not have any common structural features which would motivate a person of ordinary skill to combine them. Even if combined there would not be any hint of the effect of the said compounds on the biosynthesis of COX 2- and NFκb.

For the reasons expressed above, it is urged that the prior art references cited by the examiner either singly or in combination fail to anticipate or suggest the present

invention as defined by the amended claims. Accordingly, a *prima facie* case of obviousness has not been established by the examiner, and the rejection under 35 USC § 103 should be withdrawn.

Attached is a check for $110.00 to cover the one month extension fee.

Please charge any shortage in fees due in connection with the filing of this paper, including Extension of Time fees to Deposit Account No. 11-0345. Please credit any excess fees to such account.

Respectfully submitted,

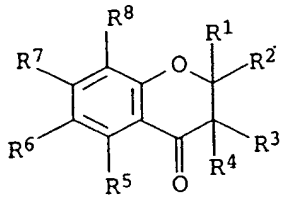
KEIL & WEINKAUF

Daniel S. Kim
Reg. No. 51,877

1350 Connecticut Ave., N.W.
Washington, D.C. 20036
(202)659-0100
DSK/kas

VERSION WITH MARKINGS TO SHOW CHANGES MADE:

1. (currently amended) A composition for inhibiting COX-2 biosynthesis or COX-2- and NFκB-biosynthesis comprising a therapeutically effective amount of the compound of the formula I

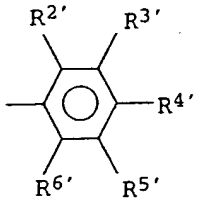


I

wherein R^1 and R^4 represent either Hydrogen or together a bond,

R^5, R^6, R^7, R^8 represent independently of each other Hydrogen, Hydroxy or Methoxy; in addition R^7 represents a sugar substituent ~~like glucoside, rutinosid, manno-gluco-pyransyl, apropsylglucoside~~,

R^2 and R^3 represent Hydrogen, Hydroxy, Methoxy or



, wherein $R^{2'}$, $R^{3'}$, ~~$R^{4'}$~~, $R^{5'}$, and $R^{6'}$ are independently or each other Hydrogen, Hydroxy or Methoxy, wherein $R^{4'}$ is H, flavone, 5-OH-flavone, 7-OH-flavone and 7,8-(OH)2-flavone, with the proviso, that R^2 or R^3 is represented by the optionally substituted Phenyl-ring and a ~~pharmaceutrically~~ pharmaceutically acceptable carrier.

3. (currently amended) A method for inhibiting COX-2 biosynthesis or COX-2

biosynthesis and NFxB biosynthesis in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 1.

4. (currently amended) A method for inhibiting COX-2 biosynthesis or COX-2 biosynthesis and NFxB biosynthesis in a patient comprising administering to a patient in need of such treatment a therapeutically effective amount of a compound of claim 2.